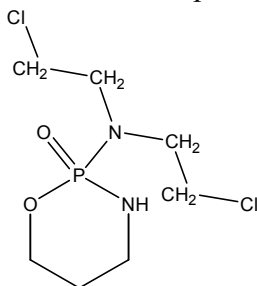


CYCLOPHOSPHAMIDE

CAS No. 50-18-0

First Listed in the *First Annual Report on Carcinogens*



CARCINOGENICITY

Cyclophosphamide is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC S.4, 1982; IARC V.26, 1981). Five epidemiological studies are available in which persons treated with cyclophosphamide for a variety of medical conditions were compared with similarly afflicted controls. These studies consistently demonstrate an excess of various neoplasms, especially of bladder cancer and leukemia, in the treated groups (IARC S.4, 1982; IARC V.26, 1981; IARC S.7, 1987).

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of cyclophosphamide in experimental animals (IARC V.9, 1975; IARC V.26, 1981; IARC S.4, 1982; IARC S.7, 1987). When administered in drinking water, cyclophosphamide induced transitional cell carcinomas and papillomas of the urinary bladder and neurogenic sarcomas arising from the peripheral nerves in rats of both sexes. When administered by subcutaneous injection, cyclophosphamide induced mammary carcinomas, lymphomas and lymphoreticular neoplasms, pulmonary adenomas and sarcomas, squamous cell carcinomas (at the site of injection), and ovarian carcinomas in mice. When administered by intravenous injection, cyclophosphamide induced sarcomas of the peritoneal cavity, reticulum cell sarcomas, and hemangioendotheliomas in various organs, in male rats (IARC V.26, 1981; IARC S.7, 1987).

PROPERTIES

Cyclophosphamide is an odorless or almost odorless fine white crystalline powder. It is soluble in water and slightly soluble in alcohol, benzene, ethylene glycol, carbon tetrachloride, and dioxane and sparingly soluble in diethyl ether and acetone. When heated to decomposition, it emits very toxic fumes of hydrochloric acid and other chlorinated compounds, nitrogen oxides (NO_x), and phosphorus oxides (PO_x). It is available in the United States as a grade containing 95%-105% active ingredient.

USE

Cyclophosphamide is a widely used synthetic antineoplastic drug for treating malignant lymphoma, multiple myeloma, leukemias, and other malignant diseases. Researchers have tested cyclophosphamide as an insect chemosterilant and for use in the chemical shearing of sheep (IARC V.26, 1981).

PRODUCTION

Cyclophosphamide is not produced domestically, and no data were available on the quantities imported (IARC V.26, 1981). The *1998 Chemical Buyers Directory* lists three suppliers of the compound, and *Chemcyclopedia 98* names two suppliers (Tilton, 1997; Rodnan, 1997). One U.S. company has formulated and marketed the drug since 1959 (IARC V.26, 1981). Total U.S. sales were reported to be about 1,300 lb in 1975 (IARC V.9, 1975).

EXPOSURE

The primary routes of potential human exposure to cyclophosphamide are inhalation, dermal contact, ingestion, and injection. FDA estimates that 200,000 to 300,000 patients were treated with cyclophosphamide in 1979. The adult dosage is usually 1 to 5 mg/kg of body weight daily or 10 to 15 mg/kg administered intravenously every 7 to 10 days. Occupational exposure potentially may occur during the packaging or formulation of the pharmaceutical. Health professionals who handle this drug (for example, pharmacists, nurses, and physicians) may possibly be exposed during drug preparation, administration, or cleanup; however, the risks can be avoided through the use of appropriate containment equipment and work practices (Zimmerman et al., 1981). A recent investigation has found that the exposure of hospital personnel to cyclophosphamide can be reduced through an easily performed procedure using a readily available reagent in the hospital environment. This is sodium hypochlorite, NaOCl, at 5.25% (household chlorine bleach). No mutagenic residues are generated by the treatment, and complete degradation occurs after one hour (Hansel et al., 1997). The National Occupational Exposure Survey (1981-1983) estimated that a total of 27,171 workers, including 18,623 women, potentially were exposed to cyclophosphamide (NIOSH, 1984).

REGULATIONS

EPA regulates cyclophosphamide under the Resource Conservation and Recovery Act (RCRA) and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). EPA established a reportable quantity (RQ) of 1 lb and proposed an adjustment of the RQ for cyclophosphamide under CERCLA to 10 lb. The final rule adjusts the RQ from 1 lb to 10 lb. Cyclophosphamide is considered a hazardous constituent of waste and is subjected to reporting requirements under RCRA. FDA regulates cyclophosphamide under the Food, Drug, and Cosmetic Act (FD&CA), subjecting it to drug labeling requirements for human prescription drugs. FDA also regulates the packaging of drugs containing cyclophosphamide; compatibility studies must be submitted when the chemical is packed in a plastic immediate container. OSHA regulates cyclophosphamide as a chemical hazard in laboratories and under the Hazard Communication Standard. Regulations are summarized in Volume II, Table A-19.